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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/653,277	08/31/2000	E. Antonio Chiocca	0609.4880002/JAG/KRM	4747

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[REDACTED] EXAMINER

WOITACH, JOSEPH T

[REDACTED] ART UNIT

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1632

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14

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	09/653,277	CHIOCCA ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Joseph Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 10 June 2002.
- 2a) This action is **FINAL**.      2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 1-36 is/are pending in the application.
- 4a) Of the above claim(s) 4-12 and 34-36 is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 1-3 and 13-33 is/are rejected.
- 7) Claim(s) \_\_\_\_\_ is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) The proposed drawing correction filed on \_\_\_\_\_ is: a) approved b) disapproved by the Examiner.  
 If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

#### Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
 a) All b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
 \* See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
 a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                  | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____  |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)         | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____                                    |

**DETAILED ACTION**

This application filed August 31, 2000, claims benefit to provisional application 60/151,621, filed August 31, 1999.

***Election/Restriction***

Applicant's election with traverse of Group I, claims 1-3, 13-33 in Paper No. 13 is acknowledged. The traversal is on the ground(s) that: citing MPEP 803, Applicants argue that the search for all the groups would not constitute an undue burden. Further, citing MPEP 808.01, Applicants argue that the inventions are related because they share at minimum related elements shared by the Herpes vectors encompassed by the claims. This is not found persuasive because for a proper restriction one of two standards must be met: 1) the inventions must be independent or distinct, and 2) there must be a serious burden on the examiner if restriction is not required of a proper restriction has been met (MPEP 806.04 and 808.02). In this case, Applicant does not contest that the inventions are not distinct, only that they are related. Further, MPEP 808.02 states that 'the Examiner, in order to establish reasons for inciting upon restriction, must show by appropriate explanation of one of the following: (A) Separate classification, (B) separate status in the art when classifiable together, or (C) a different field of search'. First, groups I-II and III have different classifications. Groups I and II have the same classification, however it should be noted that classification is used only in searching of the patent databases. Classification should not be construed as the sole criteria of a field of search. In the instant case,

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each of the alterations gives rise to a vector with different characteristics unique to each alteration, and would not be obvious one over the other. A search for one alteration would not provide for the identification of a second different alteration. Each modification encompassed by the claims would require a separate and unique search.

The requirement is still deemed proper and is therefore made **FINAL**.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

As noted in Applicants' response, claim 4 encompasses limitations which are appropriately restricted to Group II. This error was corrected in the file copy of the Restriction Requirement, however it was not noted in Applicants' copy. Examiner wishes to apologize for any inconvenience this may have caused Applicants.

Claims 1-36 are pending. Claims 4-12 and 34-36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 13. Claims 1-3 and 13-33 are currently under examination.

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***Information Disclosure Statement***

The information disclosure statement filed November 1, 2000, paper number 3, fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

***Claim objections***

Claims 13 and 30 are objected to for the following informalities: the claims contain acronyms for genes/promoters which are not specifically defined in the specification. When not specifically defined in the specification, the first presentation of an abbreviated term should be denoted by setting forth the full name indicating the term to be used subsequently. Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15, 24 and 32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled

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in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention consists of a specific herpes viral mutant Myb34.5 and methods drawn to the use of this vector. Because the specific vector is specifically recited and claimed, and the method specifically require the use of the herpes Myb34.5 mutant to practice, the Myb34.5 vector is essential to the claimed invention. Therefore, it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. It is noted that the specification provides for the general overview of how the Myb34.5 was generated, however specific sequence information and/or evidence of what the specific characteristics of the resulting vector are not presented. There is no clear evidence that the exact polynucleotide sequences of the Myb34.5 vector can be regenerated following the general outline provided in the present specification, therefore, it is not obtainable by the public. Because the Myb34.5 vector is not obtainable or available, the requirements of 35 U.S.C. 112, regarding "how to make", may be satisfied by a deposit of Myb34.5 vector. The specific construct and inherent properties of Myb34.5 can not be determined given the evidence of record, therefore deposit of the Myb34.5 is required. If a deposit was made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific cell lines have been deposited under the Budapest Treaty and that the cell lines will be irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement.

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If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that

- (a) during the pendency of this application, access to the invention will afforded to the Commissioner upon request;
- (b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;
- (c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request of for the effective life of the patent, whichever is longer; and,
- (d) a test of viability of the biological material at the time of deposit (see 37 CFR 1.807); and,
- (e) the deposit will be replaced if it should ever become inviable.

Claims 1-3 and 13-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating tumorigenic disease of the central nervous system and perfuse metastatic liver and colon cancer cells in a mammal comprising administering herpes mutant comprising: (a) an inactivating alteration in the  $\gamma$ 34.5 gene and (b) an insertion of a  $\gamma$ 34.5 gene under operatively linked to a B-myb promoter, does not reasonably provide enablement for treatment of other types of neoplastic cells or the use of other promoters.

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The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The invention is drawn broadly to the killing of any type of neoplastic cell. It is noted that the specification does not describe why one of skill in the art would practice or perform the methodology *in vitro* to kill neoplastic cells, and the general summary of the invention supports that the method is practiced in a subject. Therefore, the only substantial use proposed for the

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herpes mutants encompassed by the product claims is for the killing of neoplastic cells in a subject. The basis of the instant rejection focuses on two limitations recognized in the art for the use of the instantly claimed invention. First, mutant herpes vectors are known to infect only the cells of the central nervous system and metastatic liver and colon cancer cells, and second, the necessary teaching to use of the breadth of promoters is not adequately supported in the present specification.

Initially, it is noted that the general teachings of the present specification and the working example provides adequate evidence that a mutant herpes vector containing the  $\gamma$ 34.5 operatively linked to the B-myb promoter can unexpectedly be used to kill neuronal and metastatic cancer cells in an animal model. However, because of the limited capacity of normal herpes vectors to infect other cell types, the use of this broadly claimed class of vectors is limited to use in the infection and killing of neuronal and metastatic liver and colon cells. For example, Markowitz et al. (J. Virol. 71:5560-5569) review the distribution  $\gamma$ 34.5 single mutant herpes vectors clearly teaching the range and distribution of herpes vectors is limited to the central nervous system cells. The present specification teaches that when the Myb34.5 vector was administered to an animal model comprising perfuse metastatic liver and colon cancer cells, that these cells were effectively targeted and killed. However, injection of other herpes virus, such as HSV-1, and other herpes mutants did not result in the same cells being infected, and further, the herpes DNA could not be detected in any of the other tissues tested (specification, page 84, lines 15-25). Yoon et al. (FASEB, 2000) support this observation teaching that perfuse metastatic liver cancer

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cells were effectively infected with the mutant herpes viral vector, however other tissues tested such as the lung did not demonstrate herpes infection nor any cytopathic effects (page 309; second column). The present invention relies on the oncolytic activity of the mutant herpes vector to affect the killing of a cell in a subject. Therefore, a requirement of the vectors encompassed by the claims is the necessity to infect the target cells of interest. In the instant case, the present specification does not provide the necessary teaching to change the tropism of a herpes vector, therefore, the use of such vectors is limited to the delivery and killing of cells of the central nervous system and cells derived from metastatic liver and colon cancer.

With respect to the broad range of promoters encompassed by the claims, it is recognized that the art and the present specification provides a general teaching of genes which are up-regulated in neoplastic cells, however beyond the specific B-myb promoter specifically taught in the instant specification, the specification fails to provide the necessary guidance for the use of the broad class of promoters claimed. First, because of the limitation of infectivity of the mutant herpes virus vectors recognized in the art, only promoters which are specifically active in transformed cells of neural origin could be used in the context of the present invention. Second, the mere observation that a gene is up-regulated in a transformed cell is not an indication that the promoter taken out of context of the genome will function in the same manner. For example, Bennett *et al.* (Oncogene 13:1073-1082) teach that the B-myb promoter requires various promoter elements to silence expression of reporter gene in cultured cells. Additionally, any promoter is specifically affected by the milieu of the cell in which it is present. In the instant

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case, the simple recitation of a cell-specific or tumor-specific promoter does not provide the necessary guidance required to practice the claimed invention. The specification is silent with respect to specific guidance for other promoters besides the B-myb promoter to affect expression in neoplastic cells. Further, the specification does not provide the specific guidance on what portions of any other particular promoter one should use and in what types of neoplastic cells one should use said promoters.

The courts have stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in patent application. See *Ex parte Maizel* 27 USPQ2d 1662 . In the instant case, herpes vectors are known only to infect the cells of central nervous system and metastatic cells of liver and colon origin. Further, the mere recitation of promoters which broadly meet the functional language in light of their endogenous expression does not provide for their use in the artificial context of a vector. In light of these limitations known in the art, it would have required undue experimentation for one skilled in the art to make and/or use the claimed inventions as broadly claimed.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

***Claim Rejections - 35 USC § 103***

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The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 13, 14, 16-23, 25-31 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martuza *et al.* (US Patent 5,585,096), Pyles *et al.* (WO 98/42195), Chou *et al.* (Science, 1990), Chambers *et al.* (PNAS, 1995) and Kram *et al.* (Human Gene Therapy, 1997).

The present invention is drawn to mutant herpes vectors and use of said vectors to kill neoplastic cells. The specific mutant herpes vector encompassed by the present claims comprises an alteration in both copies of the  $\gamma$ 34.5 gene and insertion of a  $\gamma$ 34.5 gene operatively linked to a cell specific promoter. At the time of filing, Martuza *et al.* and Pyles *et al.* each teach mutant herpes vectors wherein the  $\gamma$ 34.5 gene is disrupted (also termed the ICP34.5 gene). Additionally, other alterations to the vector are taught such introducing a second disruption in the herpes vector to decrease the revertant rate of the vector, thereby increasing the safety. Further, the introduction of heterologous transgenes is taught to increase the effectiveness of the vectors in

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killing tumor cells. In particular, it is proposed that heterologous transgenes which will make the cell more sensitive to combined radio- or chemo-therapy should be introduced, for use in combined therapies/treatments of a subject. Each of Martuza *et al.* and Pyles *et al.* provide working examples of the effectiveness of said herpes vectors to effectively infect and kill tumor cells in an animal model. Martuza *et al.* and Pyles *et al.* teach the addition of secondary genes for the increased effectiveness of the herpes vector, however they do not specifically teach to express the  $\gamma$ 34.5 gene which has been removed. At the time of the claims invention Kramm *et al.* teach that the herpes vectors taught by Martuza *et al.* and Pyles *et al.* while effective *in vitro*, are not as effective in killing cells *in vivo* because of the lack of  $\gamma$ 34.5 and inability to effectively replicate (see abstract). The  $\gamma$ 34.5 gene is known to affect the virulence of the herpes virus. Specifically, Chou *et al.* teach that the  $\gamma$ 34.5 gene is non-essential to growth in culture, however affects the proliferation of the virus *in vivo*. This is further supported by observations of Chambers *et al.* who teach that the  $\gamma$ 34.5 is responsible for enhancing the viral burst size of infected cells. In summary, at the time of the claimed invention herpes vectors with alterations in the  $\gamma$ 34.5 gene were known, however they were demonstrated to be less effective in their tumocidal effect than vectors which contain the  $\gamma$ 34.5 gene. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the claimed invention to provide for the selective expression of the  $\gamma$ 34.5 gene in mutant herpes vectors. To maintain the safety of the herpes vector and at the same time increase the effectiveness of tumocidal activity, one of ordinary skill in the art would have provided for the expression of the  $\gamma$ 34.5 gene only in

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the neoplastic cells. One of ordinary skill in the art would have been motivated to provide the exogenous expression of the  $\gamma$ 34.5 gene selectively in tumor cells to maintain the safety to normal cells and increase the activity and specificity of the vectors ability to destroy neoplastic cells *in vivo*. Given the effectiveness of the mutant herpes vectors known in the art, there would have been a reasonable expectation of success to increase their effectiveness by providing the expression of  $\gamma$ 34.5 gene.

Thus, the claimed invention, as a whole was *prima facie* obvious absent to the evidence to the contrary.

### ***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist Pauline Farrier whose telephone number is (703)305-3550.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers

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must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Joseph T. Woitach

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